

### **REMARKS/ARGUMENTS**

#### **Status of the Claims**

Claims 1 and 16 have been amended. Support for these amendments can be found throughout the specification, as described below. Therefore, no new matter has been added by way of claim amendment. Entry of these amendments into the above-identified application is respectfully requested.

Claims 1 and 16 have been amended to more particularly recite the patient population to be treated by adding a patient identification step to the methods as claimed. Specifically, claims 1 and 16 have been amended to recite the step: "identifying a patient with a traumatic central nervous system injury." Support for this claim amendment may be found throughout the specification and original claims where treatment following traumatic brain injury to patients in need thereof is described using a therapeutically effective amount of allopregnanolone (e.g., page 3, lines 10-18; p. 5, lines 4-7; p. 6, line 17 to p. 7, line 18; p. 12, line 1 to p. 13, line 1; and claims 1 and 16 as filed).

These claim amendments were not presented earlier as Applicants earnestly believed that the previously presented claims recited patentable subject matter. The Examiner is respectfully requested to enter these claim amendments to further prosecution or to prepare the application for appeal.

Claims 1-12 and 14-20 are pending in the application. Reexamination and reconsideration of the claims are respectfully requested in view of the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

#### **The Rejection of the Claims Under 35 U.S.C. §102 Should Be Withdrawn**

Claims 1-12 and 15-20 are rejected under 35 U.S.C. §102(b) as being anticipated by Roof *et al.* (1997) *Molecular and Chem. Neuropathology* 31:1-11. Claims 1-12 and 15-20 are also rejected under 35 U.S.C. §102(b) as being anticipated by Roof *et al.* (1992) *Restoration of Neurology and Neuroscience* 4:425-427. Because these rejections are similar in nature, they will be addressed together. These rejections are respectfully traversed.

The Roof *et al.* (1992) reference teaches that the administration of progesterone to rats following a medial frontal cortex contusion reduces brain edema. Roof *et al.* (1997) administered progesterone to rats following a medial frontal cortex contusion and found that the brains of progesterone treated rats contained approximately one-third of the 8-isoPGF<sub>2α</sub> found in control rats. The Roof *et al.* (1997) reference goes on to state that this data supports that progesterone has antioxidant effects. None of these references by Roof *et al.* teach the methods of the present claims, namely the administration of a pharmaceutical composition comprising allopregnanolone to a patient identified as having a traumatic central nervous system injury.

The Examiner maintains the rejection of claims 1-12 and 15-20 as being inherently anticipated by the Roof *et al.* references. The Examiner states that allopregnanolone is an old and well-known progesterone metabolite, which is necessarily produced in the patient's body upon ingestion of progesterone, and thereby concludes that "Roof's steps are thus the same as the instant method steps..." (page 4, paragraph 3 of 11/04/04 Office Action). In support of this position, the Examiner continues to cite *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373 (Fed. Cir. 2003). As described below, *Schering* is not applicable in the present case and actually instructs patent practitioners to draft claims like those pending in the present application.

*Schering* dealt with a patent that claimed descarboethoxyloratadine (DCL), a non-drowsy antihistamine compound. *Id.* at 1376. The relevant issue before the court was whether composition claims drawn to DCL were novel in view of evidence that DCL was a metabolite formed naturally in the human body upon ingestion of the parent compound loratidine, coupled with a prior art patent claiming loratidine. *Id.* at 1375. In view of the evidence, the *Schering* court held that composition claims drawn to DCL were inherently anticipated. *Id.* at 1381. Applicants note, however, that the *Schering* court specifically stated that their conclusion on inherent anticipation "does not preclude patent protection for metabolites of known drugs. With proper claiming, patent protection is available for metabolites of known drugs." *Id.* In fact, the court stated that in cases such as the one before it where the prior art did not disclose the direct administration of a metabolite to a patient, a claim strategy that would prove successful in overcoming the disclosure of its parent compound would be to "claim a method of administering the metabolite or the corresponding pharmaceutical composition." *Id.*

Turning to the instant case, the Roof *et al.* references teach only the administration of progesterone to a subject to treat a traumatic brain injury. The claims of the present invention are not drawn toward compositions of either progesterone or its metabolite allopregnanolone. Instead, the present claims are drawn to a novel method of use for the metabolite allopregnanolone. The present claims are therefore the specific type of claims envisioned by the *Schering* court as a patentable use of a metabolite in view of a prior disclosure of its parent compound.

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently. *Id.* at 1377; *see also Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991); *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 630 (Fed. Cir. 1987). The Roof *et al.* references do not disclose administration of a pharmaceutical composition comprising allopregnanolone to a patient identified as having a traumatic central nervous system injury, and therefore do not explicitly meet this limitation of the present claims. In fact, the Examiner has acknowledged that the prior art does not expressly disclose the employment of allopregnanolone in a method for treating a central nervous system injury or for decreasing neurodegeneration in a subject following a traumatic CNS injury (page 3, paragraph 2 of Office Action mailed July 1, 2003). This limitation is also not inherently disclosed by Roof *et al.* since, as stated in *Schering*, a method of administering a pharmaceutical compound comprising a metabolite to a patient is not inherently anticipated by a prior art disclosure of the administration of the parent compound to a patient. Therefore, Applicants assert that the present claims are not anticipated by the Roof *et al.* references.

Because the Roof *et al.* references do not explicitly or inherently disclose every limitation of the present claims, the rejections under 35 U.S.C. §102(b) have been traversed and should be withdrawn.

Claims 1-7 and 16-17 are rejected under 35 U.S.C. §102(b) as being anticipated by Gee *et al.* (RE 35,517). This rejection is respectfully traversed.

Gee *et al.* discloses methods of modulating brain excitability through the administration of progesterone metabolites such as allopregnanolone to patients suffering from stress, anxiety,

and seizure activity. The Examiner cites Hernandez *et al.* (1997) *Neurology* 48:803-803 as teaching that "seizures are known to result from traumatic brain injury" and concludes that Gee *et al.* is teaching the administration of allopregnanolone to the same patient population as set forth in claims 1-7, 13 and 16-17. However, in spite of the fact that post-traumatic epilepsy can occur following traumatic brain injury, Gee *et al.* does not explicitly or inherently disclose the administration of allopregnanolone to the same patient population as in the present claims.

Per the Examiner's suggestion set forth in the February 8, 2005 interview, claims 1 and 16 have been amended to more clearly recite the patient population to be treated by including the step: "identifying a patient with a traumatic central nervous system injury." As stated on page 6, lines 17-23 of the specification, "[a] traumatic injury to the CNS is characterized by a physical impact to the central nervous system" (emphasis added). The Gee *et al.* reference does not explicitly or inherently disclose the administration of a pharmaceutical composition comprising allopregnanolone to a patient identified as having a traumatic central nervous system injury (i.e., a physical impact to the central nervous system). The fact that post-traumatic epilepsy can occur following traumatic brain injury as disclosed in Hernandez *et al.* does not mean that the identification of a patient suffering from seizure activity is the same as the identification of a patient with a traumatic central nervous system injury. Therefore, Applicants assert that the present claims are not anticipated by the Gee *et al.* reference.

Because the Gee *et al.* reference does not explicitly or inherently disclose every limitation of the present claims, in particular the administration of a pharmaceutical composition comprising allopregnanolone to a patient identified as having a traumatic central nervous system injury, the rejection under 35 U.S.C. §102(b) has been traversed and should be withdrawn.

Claims 1-7 and 12 are rejected under 35 U.S.C. §102(b) as being anticipated by Tauboll *et al.* (1993) *Epilepsy Research* 14:17-30. This rejection is respectfully traversed.

The Tauboll *et al.* reference teaches that administration of allopregnanolone increases seizure threshold in cats in a dose dependant manner when seizures are produced via an electrical stimulation in the primary visual cortex. The Examiner again cites Hernandez *et al.* as teaching that seizures are known to result from traumatic brain injury and concludes that Tauboll *et al.*

teach the administration of allopregnanolone to the same patient population as set forth in claims 1-7 and 12. However, in a manner similar to the rejection based on Gee *et al.* described above, Tauboll *et al.* does not explicitly or inherently disclose the administration of allopregnanolone to the same patient population as in the present claims.

As described above, claims 1 and 16 have been amended to more clearly recite the patient population to be treated. As with the Gee *et al.* reference, the Tauboll *et al.* reference also does not explicitly or inherently disclose the administration of a pharmaceutical composition comprising allopregnanolone to a patient identified as having a traumatic central nervous system injury. The fact that post-traumatic epilepsy can occur following traumatic brain injury does not mean that the identification of a patient suffering from seizure activity is the same as the identification of a patient with a traumatic central nervous system injury. Therefore, Applicants assert that the present claims are not anticipated by the Tauboll *et al.* reference.

Because the Tauboll *et al.* reference does not explicitly or inherently disclose every limitation of the present claims, in particular the administration of a pharmaceutical composition comprising allopregnanolone to a patient identified as having a traumatic central nervous system injury, the rejection under 35 U.S.C. §102(b) has been traversed and should be withdrawn.

#### The Rejection of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claim 14 is rejected under 35 U.S.C. §103(a) as being obvious in light of the Roof *et al.* or Gee *et al.* references in view of U.S. Patent 5,068,226 (Weinshenker *et al.*). This rejection is respectfully traversed.

Claim 14 is directed to a method of treating a patient identified as having a traumatic central nervous system injury through the administration of a pharmaceutical composition comprising allopregnanolone and cyclodextrin as a carrier. In the rejection of this claim for obviousness, the Examiner alternatively cites the Roof *et al.* or Gee *et al.* references as primary references and cites the Weinshenker *et al.* reference as a secondary reference. The disclosures of the Roof *et al.* and Gee *et al.* references have been described above. Weinshenker *et al.* discloses that cyclodextrins are known to be useful carriers for improving the delivery of active agents such as steroids such as progesterone and prednisolone.

One of the necessary elements for establishing a *prima facie* case of obviousness is that the prior art references must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Further, any suggestion to modify the teachings of the prior art must be found in the prior art itself, not in Applicants' disclosure. *In re Dow Chemical*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). As discussed above, the Roof *et al.* and Gee *et al.* references do not explicitly or inherently disclose the administration of a pharmaceutical composition comprising allopregnanolone to a patient identified as having a traumatic central nervous system injury. Further, none of these primary references suggest to one of skill in the art to modify their teachings to meet this claim limitation. As stated in the 132 declaration filed December 19, 2003, the mechanism of action by which progesterone and allopregnanolone mediate their effects to treat a patient identified as having a traumatic central nervous system injury is unknown and one of skill would not assume progesterone and allopregnanolone have identical mechanisms of action. The Weinshenker *et al.* reference fails to address this shortcoming of the primary references and is cited by the Examiner solely for its disclosure that cyclodextrins may be useful carriers for steroids. Therefore, the combination of Roof *et al.* or Gee *et al.* with Weinshenker *et al.* fails to teach or suggest all of the limitations of claim 14.

Applicants also maintain that this obviousness rejection amounts to hindsight reconstruction of the claimed invention. None of the cited references would guide one of skill in the art to select allopregnanolone from among the multitude of progesterone metabolites and administer this compound to a patient identified as having a traumatic central nervous system injury. Only through hindsight and with knowledge of the present application would one select references at random that mention various aspects of the claimed invention. This is an improper standard. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988); see also *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (ruling that it is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art to render it obvious).

Because the combination of Roof *et al.* or Gee *et al.* with Weinshenker *et al.* fails to teach or suggest all of the limitations of claim 14, and because the Examiner has used impermissible

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hindsight reconstruction in the selection of references that form the basis of this rejection, a *prima facie* case of obviousness has not been established. Accordingly, the rejection under 35 U.S.C. §103(a) should be withdrawn.

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### CONCLUSION

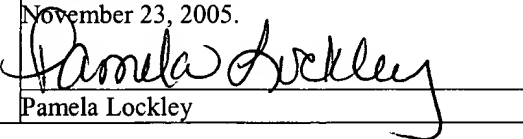
In view of the aforementioned remarks, Applicant respectfully submits that the rejections of the claims under 35 U.S.C. §§102(b) and 103(a) are overcome. Accordingly, the present application is now in condition for allowance. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



Edward R. Ergenzinger  
Registration No. 47,549

<b>Customer No. 00826</b> <b>ALSTON &amp; BIRD LLP</b> Bank of America Plaza 101 South Tryon Street, Suite 4000 Charlotte, NC 28280-4000 Tel Raleigh Office (919) 862-2200 Fax Raleigh Office (919) 862-2260	<b>CERTIFICATE OF MAILING</b> I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on November 23, 2005.  Pamela Lockley
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